

SEQUENCE LISTING

<110> DOI, Hirofumi
 SAITO, Ken

<120> Inhibition of Nerve Cell Death by Inhibiting Degradation of SHC3, ATF6 or CREBL1 by HtrA2 and Method of Ameliorating Neurodegenerative Diseases

<130> 3190-088

<140> US Unassigned
 <141> 2005-12-29

<150> PCT/JP2004/014378
 <151> 2004-09-30

<150> JP P2003-342588
 <151> 2003-09-30

<160> 37

<170> PatentIn version 3.1

<210> 1
 <211> 1377
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> DNA that codes for HtrA2 precursor protein

<400> 1
 atggctgcgc cgagggcggg gcggggtgca ggctggagcc ttcgggcatg gcgggctttg 60
 gggggcattc gctgggggag gagaccccggt ttgacccttg acctccgggc cctgctgacg 120
 tcaggaactt ctgacccccg ggcccgagtg acttatggga ccccagttct ctggggcccg 180
 ttgtctgttg gggtcactga accccgagca tgcctgacgt ctgggacccc ggggtccccg 240
 gcacaactga ctgcggtgac cccagatacc aggacccggg aggcctcaga gaactctgga 300
 acccggttcgc gcgcgtggct ggcggtggcg ctgggcgctg ggggggcagt gctgttgttg 360
 ttgtggggcg ggggtcgggg tcctccggcc gtcctcgccg ccgtccctag cccgccgccc 420
 gcttctcccc ggagtcagta caacttcatt gcagatgttg tggagaagac agcacctgcc 480
 gtggtctata tcgagatcct ggaccggcac cctttcttgg gccgcgaggt ccctatctcg 540
 aacggctcag gattcgtggt ggctgccgat gggctcattg tcaccaacgc ccatgtggtg 600
 gctgatcggc gcagagtccg tgtgagactg ctaagcggcg acacgtatga ggccgtggtc 660
 acagctgttg atcccgtggc agacatcgca acgctgagga ttcagactaa ggagcctctc 720
 cccacgctgc ctctgggacg ctcagctgat gtccggcaag gggagtttgt tgttgccatg 780
 ggaagtcctt ttgactgca gaacacgata acatccggca ttgttagctc tgctcagcgt 840
 ccagccagag acctgggact cccccaacc aatgtggaat acattcaaac tgatgcagct 900

```

attgattttg gaaactctgg aggtcccctg gttaacctgg atggggaggt gattggagtg      960
aacaccatga aggtcacagc tggaatctcc ttgccatcc cttctgatcg tcttcgagag      1020
tttctgcata gtggggaaaa gaagaattcc tcctccggaa tcagtgggtc ccagcggcgc      1080
tacattgggg tgatgatgct gaccctgagt cccagcatcc ttgctgaact acagcttcga      1140
gaaccaagct ttcccgatgt tcagcatggt gtactcatcc ataaagtcac cctgggctcc      1200
cctgcacacc gggctggtct gcggcctggt gatgtgattt tggccattgg ggagcagatg      1260
gtacaaaatg ctgaagatgt ttatgaagct gttcgaaccc aatcccagtt ggcagtgcag      1320
atccggcggg gacgagaaac actgacctta tatgtgaccc ctgaggtcac agaatga      1377

```

```

<210> 2
<211> 458
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> HtrA2 precursor protein

```

<400> 2

```

Met Ala Ala Pro Arg Ala Gly Arg Gly Ala Gly Trp Ser Leu Arg Ala
1              5              10              15

Trp Arg Ala Leu Gly Gly Ile Arg Trp Gly Arg Arg Pro Arg Leu Thr
                20              25              30

Pro Asp Leu Arg Ala Leu Leu Thr Ser Gly Thr Ser Asp Pro Arg Ala
          35              40              45

Arg Val Thr Tyr Gly Thr Pro Ser Leu Trp Ala Arg Leu Ser Val Gly
          50              55              60

Val Thr Glu Pro Arg Ala Cys Leu Thr Ser Gly Thr Pro Gly Pro Arg
65              70              75              80

Ala Gln Leu Thr Ala Val Thr Pro Asp Thr Arg Thr Arg Glu Ala Ser
          85              90              95

Glu Asn Ser Gly Thr Arg Ser Arg Ala Trp Leu Ala Val Ala Leu Gly
          100             105             110

Ala Gly Gly Ala Val Leu Leu Leu Leu Trp Gly Gly Gly Arg Gly Pro
          115             120             125

```

Pro Ala Val Leu Ala Ala Val Pro Ser Pro Pro Pro Ala Ser Pro Arg
 130 135 140

Ser Gln Tyr Asn Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala
 145 150 155 160

Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu
 165 170 175

Val Pro Ile Ser Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu
 180 185 190

Ile Val Thr Asn Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val
 195 200 205

Arg Leu Leu Ser Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp
 210 215 220

Pro Val Ala Asp Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu
 225 230 235 240

Pro Thr Leu Pro Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe
 245 250 255

Val Val Ala Met Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser
 260 265 270

Gly Ile Val Ser Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro
 275 280 285

Gln Thr Asn Val Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly
 290 295 300

Asn Ser Gly Gly Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val
 305 310 315 320

Asn Thr Met Lys Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp
 325 330 335

Arg Leu Arg Glu Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser
 340 345 350

Gly Ile Ser Gly Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr
 355 360 365

Leu Ser Pro Ser Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe
 370 375 380

Pro Asp Val Gln His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser
385 390 395 400

Pro Ala His Arg Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile
405 410 415

Gly Glu Gln Met Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg
420 425 430

Thr Gln Ser Gln Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu
435 440 445

Thr Leu Tyr Val Thr Pro Glu Val Thr Glu
450 455

<210> 3
<211> 981
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> DNA that codes for mature HtrA2

<400> 3
atggccgtcc ctagcccgcc gcccgcttct ccccgagatc agtacaactt catcgcatat 60
gtggtggaga agacagcacc tgccgtgggc tatatcgaga tcctggaccg gcaccctttc 120
ttgggccgag aggtccctat ctggaacggc tcaggattcg tgggtggctgc cgatgggctc 180
attgtcacca acgcccattg ggtggctgat cggcgagag tccgtgtgag actgctaagc 240
ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300
aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtcccg 360
caaggggagt ttgttgttgc catgggaagt ccctttgcac tgcagaacac gatcacatcc 420
ggcattgtta gctctgtcga gcgtccagcc agagacctgg gactccccca aaccaatgtg 480
gaatacatcc aaactgatgc agctattgat tttggaaact ctggaggtcc cctgggttaac 540
ctggatgggg aggtgattgg agtgaacacc atgaaggcca cagctggaat ctcctttgcc 600
atcccttctg atcgtcttcg agagtttctg catcgtgggg aaaagaagaa ttcctcctcc 660
ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720
atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgtactc 780
atccataaag tcatcctggg ctcccctgca caccgggctg gtctgcggcc tgggtgatgtg 840
atcttgccca ttggggagca gatggtacaa aatgctgaag atgtttatga agctgttcga 900
acccaatccc agttggcagt gcagatccgg cggggacgag aaacactgac cttatatgtg 960

accctgagg tcacagaatg a

981

<210> 4
<211> 326
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> mature HtrA2

<400> 4

Met Ala Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn
1 5 10 15

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile
20 25 30

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser
35 40 45

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn
50 55 60

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser
65 70 75 80

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp
85 90 95

Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro
100 105 110

Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met
115 120 125

Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser
130 135 140

Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val
145 150 155 160

Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly Asn Ser Gly Gly
165 170 175

Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys
180 185 190

Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu
195 200 205

Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly
210 215 220

Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser
225 230 235 240

Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln
245 250 255

His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg
260 265 270

Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met
275 280 285

Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln
290 295 300

Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val
305 310 315 320

Thr Pro Glu Val Thr Glu
325

<210> 5
<211> 981
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide consisting of the same base sequence of SEQ ID NO:
3 wherein the nucleotide of position 520 is g

<220>
<221> misc_feature
<223> DNA that codes for mature HtrA2 (S306A)

<400> 5
atggcgtcc ctagcccgcc gcccgcttct ccccgagtc agtacaactt catcgcat 60
gtggtggaga agacagcacc tgccgtggtc tatatcgaga tcctggaccg gcaccctttc 120
ttgggccgag aggtccctat ctcgaacggc tcaggattcg tgggtggctgc cgatgggctc 180
attgtcacca acgcccattg ggtggctgat cggcgagag tccgtgtgag actgctaagc 240
ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300
aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtccgg 360

```

caaggggagt ttgttggtgc catgggaagt ccctttgcac tgcagaacac gatcacatcc 420
ggcattgtta gctctgctca gcgtccagcc agagacctgg gactcccca aaccaatgtg 480
gaatacattc aaactgatgc agctattgat tttggaaacg ctggaggtcc cctggttaac 540
ctgggatggg aggtgattgg agtgaacacc atgaagggtca cagctggaat ctcctttgcc 600
atcccttctg atcgtcttcg agagtttctg catcgtgggg aaaagaagaa ttcctcctcc 660
ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720
atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgtactc 780
atccataaag tcatactggg ctcccctgca caccgggctg gtctgcggcc tgggtgatgtg 840
attttgcca ttggggagca gatggtacaa aatgctgaag atgtttatga agctgttcga 900
acccaatccc agttggcagt gcagatccgg cggggacgag aaacactgac cttatatgtg 960
acccctgagg tcacagaatg a 981

```

```

<210> 6
<211> 326
<212> PRT
<213> Artificial

```

```

<220>
<223> Polypeptide consisting of the same amino acid sequence of SEQ ID
      NO:4 wherein the 174th amino acid residue is substituted by Ala

```

```

<220>
<221> misc_feature
<223> mature HtrA2 (S306A)

```

```

<400> 6

```

```

Met Ala Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn
1           5           10           15

```

```

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile
20           25           30

```

```

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser
35           40           45

```

```

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn
50           55           60

```

```

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser
65           70           75           80

```

```

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp
85           90           95

```

Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro
100 105 110

Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met
115 120 125

Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser
130 135 140

Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val
145 150 155 160

Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly Asn Ala Gly Gly
165 170 175

Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys
180 185 190

Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu
195 200 205

Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly
210 215 220

Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser
225 230 235 240

Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln
245 250 255

His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg
260 265 270

Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met
275 280 285

Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln
290 295 300

Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val
305 310 315 320

Thr Pro Glu Val Thr Glu
325

<210> 7
<211> 969

<212> DNA
 <213> Artificial

 <220>
 <223> Polynucleotide consisting of the same base sequence of SEQ ID NO: 3 wherein the nucleotides of position 4-15 are deleted

 <220>
 <221> misc_feature
 <223> DNA that codes for mature HtrA2(delta AVPS)

<400> 7
 atgccgcgcg ccgcttctcc ccggagtcag tacaacttca tcgcagatgt ggtggagaag 60
 acagcacctg ccgtgggtcta tatcgagatc ctggaccggc accctttctt gggccgcgag 120
 gtccctatct cgaacggctc aggattcgtg gtggctgccc atgggctcat tgtcaccaac 180
 gcccatgtgg tggctgatcg gcgcagagtc cgtgtgagac tgctaagcgg cgacacgtat 240
 gaggccgtgg tcacagctgt ggatcccgtg gcagacatcg caacgctgag gattcagact 300
 aaggagcctc tccccacgct gcctctggga cgctcagctg atgtccggca aggggagttt 360
 gttgttgcca tgggaagtcc ctttgactg cagaacacga tcacatccgg cattgttagc 420
 tctgctcagc gtccagccag agacctggga ctccccaaa ccaatgtgga atacattcaa 480
 actgatgcag ctattgattt tggaaactct ggaggtcccc tggttaacct ggatggggag 540
 gtgattggag tgaacaccat gaaggtcaca gctggaatct cctttgccat cccttctgat 600
 cgtcttcgag agtttctgca tcgtggggaa aagaagaatt cctcctccgg aatcagtggg 660
 tcccagcggc gctacattgg ggtgatgatg ctgaccctga gtcccagcat ccttgctgaa 720
 ctacagcttc gagaaccaag ctttcccgat gttcagcatg gtgtactcat ccataaagtc 780
 atcctgggct cccctgcaca ccgggctggg ctgcccctcg gtgatgtgat tttggccatt 840
 ggggagcaga tggtaaaaa tgctgaagat gtttatgaag ctgttcgaac ccaatcccag 900
 ttggcagtgc agatccggcg gggacgagaa aactgacct tatatgtgac ccctgaggtc 960
 acagaatga 969

<210> 8
 <211> 322
 <212> PRT
 <213> Artificial

 <220>
 <223> Polypeptide consisting of the same amino acid sequence of SEQ ID NO:4 wherein the amino acid residues from the 2nd to the 5th are deleted

 <220>
 <221> misc_feature
 <223> mature HtrA2(delta AVPS)

<400> 8

Met Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn Phe Ile Ala Asp
1 5 10 15

Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile Glu Ile Leu Asp
20 25 30

Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly
35 40 45

Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn Ala His Val Val
50 55 60

Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser Gly Asp Thr Tyr
65 70 75 80

Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp Ile Ala Thr Leu
85 90 95

Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro Leu Gly Arg Ser
100 105 110

Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met Gly Ser Pro Phe
115 120 125

Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser Ser Ala Gln Arg
130 135 140

Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val Glu Tyr Ile Gln
145 150 155 160

Thr Asp Ala Ala Ile Asp Phe Gly Asn Ser Gly Gly Pro Leu Val Asn
165 170 175

Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys Val Thr Ala Gly
180 185 190

Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu Phe Leu His Arg
195 200 205

Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly Ser Gln Arg Arg
210 215 220

Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser Ile Leu Ala Glu
225 230 235 240

Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln His Gly Val Leu

245

250

255

Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg Ala Gly Leu Arg
260 265 270

Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met Val Gln Asn Ala
275 280 285

Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln Leu Ala Val Gln
290 295 300

Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val Thr Pro Glu Val
305 310 315 320

Thr Glu

<210> 9
<211> 981
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide consisting of the same base sequence of SEQ ID NO:
3 wherein the nucleotide of position 5 is g

<220>
<221> misc_feature
<223> DNA that codes for mature HtrA2 (GVPS)

<400> 9
atgggcggtcc ctagcccgcc gcccgcttct ccccgagatc agtacaactt catcgagat 60
gtggtggaga agacagcacc tgccgtggtc tatatcgaga tcctggaccg gcaccctttc 120
ttgggccgag aggtccctat ctggaacggc tcaggattcg tgggtggctgc cgatgggctc 180
attgtcacca acgcccattg ggtggctgat cggcgagag tccgtgtgag actgctaagc 240
ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300
aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtccgg 360
caaggggagt ttgttgttgc catgggaagt ccctttgcac tgcagaacac gatcacatcc 420
ggcattgtta gctctgctca gcgtccagcc agagacctgg gactcccca aaccaatgtg 480
gaatacattc aaactgatgc agctattgat tttggaaact ctggaggtcc cctggttaac 540
ctggatgggg aggtgattgg agtgaacacc atgaaggatc cagctggaat ctcctttgcc 600
atcccttctg atcgtcttcg agagtttctg catcgtgggg aaaagaagaa ttcctcctcc 660
ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720
atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgtactc 780

atccataaag tcacccctggg ctcccctgca caccgggctg gtctgcggcc tggatgatgtg 840
 attttgcca ttggggagca gatggtacaa aatgctgaag atgtttatga agctgttcga 900
 acccaatccc agttggcagt gcagatccgg cggggacgag aaacactgac cttatatgtg 960
 acccctgagg tcacagaatg a 981

<210> 10
 <211> 326
 <212> PRT
 <213> Artificial

<220>
 <223> Polypeptide consisting of the same amino acid sequence of SEQ ID NO:4 wherein the 2nd amino acid residue is substituted by Gly

<220>
 <221> misc_feature
 <223> mature HtrA2 (GVPS)

<400> 10

Met Gly Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn
 1 5 10 15

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile
 20 25 30

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser
 35 40 45

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn
 50 55 60

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser
 65 70 75 80

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp
 85 90 95

Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro
 100 105 110

Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met
 115 120 125

Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser
 130 135 140

Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val


```

acagcacctg ccgtggtcta tatcgagatc ctggaccggc accctttctt gggccgcgag      120
gtccctatct cgaacggctc aggattcgtg gtggctgccg atgggctcat tgtcaccaac      180
gcccattgtg tggtgatcg gcgcagagtc cgtgtgagac tgctaagcgg cgacacgtat      240
gaggccgtgg tcacagctgt ggatcccgtg gcagacatcg caacgctgag gattcagact      300
aaggagcctc tccccacgct gcctctggga cgctcagctg atgtccggca aggggagttt      360
gttgttgcca tgggaagtcc ctttgactg cagaacacga tcacatccgg cattgttagc      420
tctgctcagc gtccagccag agacctggga ctcccccaaa ccaatgtgga atacattcaa      480
actgatgcag ctattgattt tggaaacgct ggagggtccc tggttaacct ggatggggag      540
gtgattggag tgaacaccat gaaggtcaca gctggaatct cctttgccat cccttctgat      600
cgtcttcgag agtttctgca tcgtggggaa aagaagaatt cctcctccgg aatcagtggg      660
tcccagcggc gctacattgg ggtgatgatg ctgaccctga gtcccagcat ccttgctgaa      720
ctacagcttc gagaaccaag ctttcccgat gttcagcatg gtgtactcat ccataaagtc      780
atcctgggct cccctgcaca ccgggctggg ctgcggcctg gtgatgtgat tttggccatt      840
ggggagcaga tggtaaaaa tgctgaagat gtttatgaag ctgttcgaac ccaatcccag      900
ttggcagtgc agatccggcg gggacgagaa aactgacct tatatgtgac ccctgaggtc      960
acagaatga                                          969

```

```

<210> 12
<211> 322
<212> PRT
<213> Artificial

```

```

<220>
<223> Polypeptide consisting of the same amino acid sequence of SEQ ID
      NO:6 wherein the amino acid residues from the 2nd to the 5th are
      deleted

```

```

<220>
<221> misc_feature
<223> mature HtrA2(S306A, delta AVPS)

```

```

<400> 12

```

```

Met Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn Phe Ile Ala Asp
1           5           10           15

```

```

Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile Glu Ile Leu Asp
          20           25           30

```

```

Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly
          35           40           45

```

Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn Ala His Val Val
50 55 60

Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser Gly Asp Thr Tyr
65 70 75 80

Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp Ile Ala Thr Leu
85 90 95

Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro Leu Gly Arg Ser
100 105 110

Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met Gly Ser Pro Phe
115 120 125

Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser Ser Ala Gln Arg
130 135 140

Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val Glu Tyr Ile Gln
145 150 155 160

Thr Asp Ala Ala Ile Asp Phe Gly Asn Ala Gly Gly Pro Leu Val Asn
165 170 175

Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys Val Thr Ala Gly
180 185 190

Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu Phe Leu His Arg
195 200 205

Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly Ser Gln Arg Arg
210 215 220

Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser Ile Leu Ala Glu
225 230 235 240

Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln His Gly Val Leu
245 250 255

Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg Ala Gly Leu Arg
260 265 270

Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met Val Gln Asn Ala
275 280 285

Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln Leu Ala Val Gln
290 295 300

Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val Thr Pro Glu Val
 305 310 315 320

Thr Glu

<210> 13
 <211> 981
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide consisting of the same base sequence of SEQ ID NO:
 5 wherein the nucleotide of position 5 is g

<220>
 <221> misc_feature
 <223> DNA that codes for mature HtrA2(S306A, GVPS)

<400> 13
 atgggcgtcc ctagcccgcc gcccgcttct ccccgaggatc agtacaactt catcgcagat 60
 gtggtggaga agacagcacc tgccgtggtc tatatcgaga tcctggaccg gcaccctttc 120
 ttgggccgcg aggtccctat ctcgaaacggc tcaggattcg tggtaggctgc cgatgggctc 180
 attgtcacca acgcccattgt ggtggctgat cggcgacagag tccgtgtgag actgctaagc 240
 ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300
 aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtccgg 360
 caaggggagt ttgtttgttc catgggaagt ccctttgcac tgcagaacac gatcacatcc 420
 ggcaattgta gctctgtctc gcgtccagcc agagacctgg gactccccca aaccaatgtg 480
 gaatacatte aaactgatgc agctattgat tttggaaacg ctggaggtcc cctgggttaac 540
 ctggatgggg aggtgattgg agtgaacacc atgaaggatc cagctggaat ctcccttgcc 600
 atcccttctg atcgtctctg agagtttctg catcgtgggg aaaagaagaa ttcctcctcc 660
 ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720
 atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgtactc 780
 atccataaag tcacctctgg ctcccctgca caccgggctg gtctgcggcc tggatgatgtg 840
 attttgcca ttggggagca gatggtacaa aatgctgaag atgtttatga agctgttcga 900
 acccaatccc agttggcagt gcagatccgg cggggacgag aaacactgac cttatatgtg 960
 acccctgagg tcacagaatg a 981

<210> 14
 <211> 326
 <212> PRT
 <213> Artificial

<220>

<223> Polypeptide consisting of the same amino acid sequence of SEQ ID NO:6 wherein the 2nd amino acid residue is substituted by Gly

<220>

<221> misc_feature

<223> mature HtrA2(S306A, GVPS)

<400> 14

Met Gly Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn
1 5 10 15

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile
20 25 30

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser
35 40 45

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn
50 55 60

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser
65 70 75 80

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp
85 90 95

Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro
100 105 110

Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met
115 120 125

Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser
130 135 140

Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val
145 150 155 160

Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly Asn Ala Gly Gly
165 170 175

Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys
180 185 190

Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu
195 200 205

Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly
 210 215 220
 Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser
 225 230 235 240
 Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln
 245 250 255
 His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg
 260 265 270
 Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met
 275 280 285
 Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln
 290 295 300
 Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val
 305 310 315 320
 Thr Pro Glu Val Thr Glu
 325

<210> 15
 <211> 1785
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> DNA that codes for SHC3

<400> 15
 atgcttccac gcaccaagta taaccgcttc aggaatgact cggtgacatc ggtcgatgac 60
 cttctccaca gcctgtcggg gagcggcggc ggaggcaagg ttctggcggc gcgcgcgacc 120
 ccggcggcgg ctccctactt ggtgtccggc gaggcgctgc gcaaggcgcc cgacgatggg 180
 cccggcagcc tgggccacct gctccacaag gtgtcccacc tgaaactctc cagctcgggc 240
 ctccgcggcc tgtcgtcggc cgcccgggag cgggcggggc cgcggtcttc gggcagctgc 300
 agcgcgcca gcctggccgc cccggacggc agtgcgccct cggcgccccg cgccccggcc 360
 atgagcgccg ccaggaaggg ccggcccggc gacgagccgc tgcccaggcc ccctcggggg 420
 ggcgcgcacg ccagcgacca ggtgctgggg cccggagtca cctacgtggt caagtacttg 480
 ggggtgcattg aagtctcgcg ctcaatgagg tctcttgact tcagtacaag aacacaaatt 540
 accagggaag ccatcagccg cgtctgtgaa gctgtgcctg gtgcgaaggg agccttcaag 600

aagagaaagc ctccaagcaa aatgctgtcc agcatcttgg gaaagagcaa cctccagttt 660
gcgggaatga gcatctctct gaccatctcc acggccagtc tgaacctgcg aactccggac 720
tccaaacaga tcatagcgaa tcaccacatg cgggtccatct ccttcgcctc tgggggagac 780
ccggacacaa ctgactatgt tgcatatgtg gctaaggacc ctgttaatcg cagagcttgt 840
cacatttttg aatgctgtga tgggctggcc caggatgtca tcggctccat cggacaagcc 900
tttgagctcc ggtttaagca atatttacag tgtcctacca agattcccg c tctccatgat 960
cgaatgcaga gtctggatga gccatggacg gaagaggagg gagatggctc agaccaccca 1020
tactacaaca gcatcccaag caagatgcct cctccagggg gctttcttga tactagactg 1080
aaaccacagc cccatgctcc tgacacagcc cagtttgcag gaaaagagca gacttattac 1140
cagggaagac acttaggaga cacttttggc gaagactggc agcaaacacc ttttaaggcaa 1200
gggtcctcgg acatctacag cacgccagaa gggaaactgc acgtggcccc cacgggagaa 1260
gcacccacct acgtcaacac tcagcagatc ccaccacagg cctggccggc tgcggtcagc 1320
agtgtctgaga gcagcccaag gaaagacctc tttgacatga aaccttttga agatgtcttc 1380
aagaaccagc ccttggggcc cgtgttaagc aaggcagcct ccgtggagtg catcagccct 1440
gtgtcaccta gagccccaga tgccaagatg ctggaggaac tgcaagccga gacttggtac 1500
caaggagaga tgagcaggaa ggaggcagag gggctgctgg agaaagacgg agacttcctg 1560
gtcaggaaga gcaccaccaa cccgggctcc tttgtctcga cgggcatgca caatggccag 1620
gccaagcacc tgctgctcgt ggaccacagaa ggacagatcc ggacaaagga cagagtcttt 1680
gacagtatca gccacctcat caaccaccac ctagaaagca gcctgcccac tgtctctgca 1740
gggagtgagc tgtgtctcca gcagccagtg gagaggaagc agtga 1785

<210> 16
<211> 594
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> SHC3

<400> 16

Met Leu Pro Arg Thr Lys Tyr Asn Arg Phe Arg Asn Asp Ser Val Thr
1 5 10 15

Ser Val Asp Asp Leu Leu His Ser Leu Ser Val Ser Gly Gly Gly Gly
20 25 30

Lys Val Ser Ala Ala Arg Ala Thr Pro Ala Ala Ala Pro Tyr Leu Val

Ser Gly Glu Ala Leu Arg Lys Ala Pro Asp Asp Gly Pro Gly Ser Leu
50 55 60

Gly His Leu Leu His Lys Val Ser His Leu Lys Leu Ser Ser Ser Gly
65 70 75 80

Leu Arg Gly Leu Ser Ser Ala Ala Arg Glu Arg Ala Gly Ala Arg Leu
85 90 95

Ser Gly Ser Cys Ser Ala Pro Ser Leu Ala Ala Pro Asp Gly Ser Ala
100 105 110

Pro Ser Ala Pro Arg Ala Pro Ala Met Ser Ala Ala Arg Lys Gly Arg
115 120 125

Pro Gly Asp Glu Pro Leu Pro Arg Pro Pro Arg Gly Ala Pro His Ala
130 135 140

Ser Asp Gln Val Leu Gly Pro Gly Val Thr Tyr Val Val Lys Tyr Leu
145 150 155 160

Gly Cys Ile Glu Val Leu Arg Ser Met Arg Ser Leu Asp Phe Ser Thr
165 170 175

Arg Thr Gln Ile Thr Arg Glu Ala Ile Ser Arg Val Cys Glu Ala Val
180 185 190

Pro Gly Ala Lys Gly Ala Phe Lys Lys Arg Lys Pro Pro Ser Lys Met
195 200 205

Leu Ser Ser Ile Leu Gly Lys Ser Asn Leu Gln Phe Ala Gly Met Ser
210 215 220

Ile Ser Leu Thr Ile Ser Thr Ala Ser Leu Asn Leu Arg Thr Pro Asp
225 230 235 240

Ser Lys Gln Ile Ile Ala Asn His His Met Arg Ser Ile Ser Phe Ala
245 250 255

Ser Gly Gly Asp Pro Asp Thr Thr Asp Tyr Val Ala Tyr Val Ala Lys
260 265 270

Asp Pro Val Asn Arg Arg Ala Cys His Ile Leu Glu Cys Cys Asp Gly
275 280 285

Leu Ala Gln Asp Val Ile Gly Ser Ile Gly Gln Ala Phe Glu Leu Arg
 290 295 300

Phe Lys Gln Tyr Leu Gln Cys Pro Thr Lys Ile Pro Ala Leu His Asp
 305 310 315 320

Arg Met Gln Ser Leu Asp Glu Pro Trp Thr Glu Glu Glu Gly Asp Gly
 325 330 335

Ser Asp His Pro Tyr Tyr Asn Ser Ile Pro Ser Lys Met Pro Pro Pro
 340 345 350

Gly Gly Phe Leu Asp Thr Arg Leu Lys Pro Arg Pro His Ala Pro Asp
 355 360 365

Thr Ala Gln Phe Ala Gly Lys Glu Gln Thr Tyr Tyr Gln Gly Arg His
 370 375 380

Leu Gly Asp Thr Phe Gly Glu Asp Trp Gln Gln Thr Pro Leu Arg Gln
 385 390 395 400

Gly Ser Ser Asp Ile Tyr Ser Thr Pro Glu Gly Lys Leu His Val Ala
 405 410 415

Pro Thr Gly Glu Ala Pro Thr Tyr Val Asn Thr Gln Gln Ile Pro Pro
 420 425 430

Gln Ala Trp Pro Ala Ala Val Ser Ser Ala Glu Ser Ser Pro Arg Lys
 435 440 445

Asp Leu Phe Asp Met Lys Pro Phe Glu Asp Ala Leu Lys Asn Gln Pro
 450 455 460

Leu Gly Pro Val Leu Ser Lys Ala Ala Ser Val Glu Cys Ile Ser Pro
 465 470 475 480

Val Ser Pro Arg Ala Pro Asp Ala Lys Met Leu Glu Glu Leu Gln Ala
 485 490 495

Glu Thr Trp Tyr Gln Gly Glu Met Ser Arg Lys Glu Ala Glu Gly Leu
 500 505 510

Leu Glu Lys Asp Gly Asp Phe Leu Val Arg Lys Ser Thr Thr Asn Pro
 515 520 525

Gly Ser Phe Val Leu Thr Gly Met His Asn Gly Gln Ala Lys His Leu
 530 535 540

Leu Leu Val Asp Pro Glu Gly Thr Ile Arg Thr Lys Asp Arg Val Phe
 545 550 555 560

Asp Ser Ile Ser His Leu Ile Asn His His Leu Glu Ser Ser Leu Pro
 565 570 575

Ile Val Ser Ala Gly Ser Glu Leu Cys Leu Gln Gln Pro Val Glu Arg
 580 585 590

Lys Gln

<210> 17
 <211> 2112
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> DNA that codes for CREBL1

<400> 17
 atggcggagc tgatgctgct cagcgagatt gctgaccoga cgcgtttctt caccgacaac 60
 ctgcttagcc cggaggactg gggctctgcag aacagcacct tgtattcttg cctagatgaa 120
 gtggccgagg agcagacgca gctcttccgt tgcccggagc aggatgtccc gtttgacggc 180
 agctccctgg acgtggggat ggatgtcagc ccctctgagc ccccatggga actcctgccg 240
 atcttcccag atcttcaggt gaagtctgag ccatcttccc cctgctcttc ctctccctc 300
 agctccgagt catcgctct ctccacagag ccatccagcg aggctcttg ggtaggggag 360
 gtgctccatg tgaagacaga gtccttggca cccccactgt gtctcctggg agatgaccca 420
 acatcctcat ttgaaaccgt ccagatcaat gttatcccca cctctgatga ttcctcagat 480
 gtccagacca agatagaacc tgtctctcca tgttcttccg tcaactctga ggcctccctg 540
 ctctcagccg actcctccag ccaggctttt ataggagagg aggtcctgga agtgaagaca 600
 gagtccctgt ccccttcagg atgcctcctg tgggatgtcc cagccccctc acttgagact 660
 gtccagatca gcatggggcc atcccttgat ggctcctcag gcaaagccct gccacccgg 720
 aagccgccac tgcagcccaa acctgtagt ctaaccactg tcccaatgcc atccagagct 780
 gtgcctcca gcaccacagt ccttctgcag tccctcgtcc agccaccccc agtgtcccca 840
 gttgtcctca tccagggtgc tattcgagtc cagcctgaag ggccgggtcc ctctctacca 900
 cggcctgaga ggaagagcat cggtcccgt cctatgcttg gaaactcctg cccgcctgaa 960
 gtggatgcaa agctgctgaa gcggcagcag cgaatgatca agaaccggga gtcagcctgc 1020
 cagtcccga gaaagaagaa agagtatctg cagggactgg aggctcggct gcaagcagta 1080

```

ctggctgaca accagcagct ccgccgagag aatgctgccc tccggcggcg gctggaggcc 1140
ctgctggctg aaaacagcga gctcaagtta gggctctggaa acaggaaggt ggtctgcatc 1200
atggtcttcc ttctcttcat tgccttcaac tttggacctg tcagcatcag tgagcctcct 1260
tcagctccca tctctcctcg gatgaacaag ggggagcctc aaccccggag acacttgctg 1320
gggttctcag agcaagagcc agttcaggga gttgaacctc tccaggggtc ctcccagggc 1380
cctaaggagc cccagcccag ccccacagac cagcccagtt tcagcaacct gacagccttc 1440
cctggggggcg ccaaggagct actactaaga gacctagacc agctcttcct ctctctgat 1500
tgccggcact tcaaccgcac tgagtccttg aggcttgctg acgagttgag tggctgggtc 1560
cagcgccacc agagaggccg gaggaagatc cctcagaggg cccaggagag acagaagtct 1620
cagccacgga agaagtcacc tccagttaag gcagtcccca tccaaccccc tggaccccca 1680
gaaagggatt ctgtgggcca gctgcaacta tatcgccacc cagaccgttc gcagccagca 1740
ttcttggtat caattgaccg acgggaagac acattttatg ttgtctcttt ccgaagggac 1800
cacctgctgc tcccagccat cagccacaac aagacctccc ggccaagat gtccctggtg 1860
atgcctgcca tggcccccaa tgagaccctg tcaggccgtg gggccccggg ggactatgag 1920
gagatgatgc agatcgagtg tgaggtcatg gacaccaggg tgattcacat caagacctcc 1980
acagtgcccc cctcgctccg aaaacagcca tccccaaacc caggcaatgc cacaggtggc 2040
cccttgccag tctctgcagc cagccaggcc caccaggcct cccaccagcc cctctacctc 2100
aatcatccct aa 2112

```

```

<210> 18
<211> 703
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<223> CREBL1

```

```

<400> 18

```

```

Met Ala Glu Leu Met Leu Leu Ser Glu Ile Ala Asp Pro Thr Arg Phe
1           5           10           15

```

```

Phe Thr Asp Asn Leu Leu Ser Pro Glu Asp Trp Gly Leu Gln Asn Ser
          20           25           30

```

```

Thr Leu Tyr Ser Gly Leu Asp Glu Val Ala Glu Glu Gln Thr Gln Leu
          35           40           45

```

```

Phe Arg Cys Pro Glu Gln Asp Val Pro Phe Asp Gly Ser Ser Leu Asp

```

50

55 .

60

Val Gly Met Asp Val Ser Pro Ser Glu Pro Pro Trp Glu Leu Leu Pro
65 70 75 80

Ile Phe Pro Asp Leu Gln Val Lys Ser Glu Pro Ser Ser Pro Cys Ser
85 90 95

Ser Ser Ser Leu Ser Ser Glu Ser Ser Arg Leu Ser Thr Glu Pro Ser
100 105 110

Ser Glu Ala Leu Gly Val Gly Glu Val Leu His Val Lys Thr Glu Ser
115 120 125

Leu Ala Pro Pro Leu Cys Leu Leu Gly Asp Asp Pro Thr Ser Ser Phe
130 135 140

Glu Thr Val Gln Ile Asn Val Ile Pro Thr Ser Asp Asp Ser Ser Asp
145 150 155 160

Val Gln Thr Lys Ile Glu Pro Val Ser Pro Cys Ser Ser Val Asn Ser
165 170 175

Glu Ala Ser Leu Leu Ser Ala Asp Ser Ser Ser Gln Ala Phe Ile Gly
180 185 190

Glu Glu Val Leu Glu Val Lys Thr Glu Ser Leu Ser Pro Ser Gly Cys
195 200 205

Leu Leu Trp Asp Val Pro Ala Pro Ser Leu Gly Ala Val Gln Ile Ser
210 215 220

Met Gly Pro Ser Leu Asp Gly Ser Ser Gly Lys Ala Leu Pro Thr Arg
225 230 235 240

Lys Pro Pro Leu Gln Pro Lys Pro Val Val Leu Thr Thr Val Pro Met
245 250 255

Pro Ser Arg Ala Val Pro Pro Ser Thr Thr Val Leu Leu Gln Ser Leu
260 265 270

Val Gln Pro Pro Pro Val Ser Pro Val Val Leu Ile Gln Gly Ala Ile
275 280 285

Arg Val Gln Pro Glu Gly Pro Ala Pro Ser Leu Pro Arg Pro Glu Arg
290 295 300

Lys Ser Ile Val Pro Ala Pro Met Pro Gly Asn Ser Cys Pro Pro Glu
 305 310 315 320

Val Asp Ala Lys Leu Leu Lys Arg Gln Gln Arg Met Ile Lys Asn Arg
 325 330 335

Glu Ser Ala Cys Gln Ser Arg Arg Lys Lys Lys Glu Tyr Leu Gln Gly
 340 345 350

Leu Glu Ala Arg Leu Gln Ala Val Leu Ala Asp Asn Gln Gln Leu Arg
 355 360 365

Arg Glu Asn Ala Ala Leu Arg Arg Arg Leu Glu Ala Leu Leu Ala Glu
 370 375 380

Asn Ser Glu Leu Lys Leu Gly Ser Gly Asn Arg Lys Val Val Cys Ile
 385 390 395 400

Met Val Phe Leu Leu Phe Ile Ala Phe Asn Phe Gly Pro Val Ser Ile
 405 410 415

Ser Glu Pro Pro Ser Ala Pro Ile Ser Pro Arg Met Asn Lys Gly Glu
 420 425 430

Pro Gln Pro Arg Arg His Leu Leu Gly Phe Ser Glu Gln Glu Pro Val
 435 440 445

Gln Gly Val Glu Pro Leu Gln Gly Ser Ser Gln Gly Pro Lys Glu Pro
 450 455 460

Gln Pro Ser Pro Thr Asp Gln Pro Ser Phe Ser Asn Leu Thr Ala Phe
 465 470 475 480

Pro Gly Gly Ala Lys Glu Leu Leu Leu Arg Asp Leu Asp Gln Leu Phe
 485 490 495

Leu Ser Ser Asp Cys Arg His Phe Asn Arg Thr Glu Ser Leu Arg Leu
 500 505 510

Ala Asp Glu Leu Ser Gly Trp Val Gln Arg His Gln Arg Gly Arg Arg
 515 520 525

Lys Ile Pro Gln Arg Ala Gln Glu Arg Gln Lys Ser Gln Pro Arg Lys
 530 535 540

Lys Ser Pro Pro Val Lys Ala Val Pro Ile Gln Pro Pro Gly Pro Pro
 545 550 555 560

Glu Arg Asp Ser Val Gly Gln Leu Gln Leu Tyr Arg His Pro Asp Arg
565 570 575

Ser Gln Pro Ala Phe Leu Asp Ala Ile Asp Arg Arg Glu Asp Thr Phe
580 585 590

Tyr Val Val Ser Phe Arg Arg Asp His Leu Leu Leu Pro Ala Ile Ser
595 600 605

His Asn Lys Thr Ser Arg Pro Lys Met Ser Leu Val Met Pro Ala Met
610 615 620

Ala Pro Asn Glu Thr Leu Ser Gly Arg Gly Ala Pro Gly Asp Tyr Glu
625 630 635 640

Glu Met Met Gln Ile Glu Cys Glu Val Met Asp Thr Arg Val Ile His
645 650 655

Ile Lys Thr Ser Thr Val Pro Pro Ser Leu Arg Lys Gln Pro Ser Pro
660 665 670

Thr Pro Gly Asn Ala Thr Gly Gly Pro Leu Pro Val Ser Ala Ala Ser
675 680 685

Gln Ala His Gln Ala Ser His Gln Pro Leu Tyr Leu Asn His Pro
690 695 700

<210> 19
<211> 2013
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> DNA that codes for ATF6

<400> 19
atgggggagc cggctggggt tgccggcacc atggagtcac cttttagccc gggactcttt 60
cacaggctgg atgaagattg ggattctgct ctctttgctg aactcgggta tttcacagac 120
actgatgagc tgcaattgga agcagcaaat gagacgtatg aaaacaattt tgataatctt 180
gattttgatt tggatttgat gccttgggag tcagacattt gggacatcaa caaccaaadc 240
tgtacagtta aagatattaa ggcagaacct cagccacttt ctccagcctc ctcaagttat 300
tcagtctcgt ctctcgggtc agtggactct tattcttcaa ctacagcatgt tcttgaggag 360
ttggatttgt cttctagttc tcagatgtct cccctttcct tatatggtga aaactctaata 420
agtctctctt cagcggagcc actgaaggaa gataagcctg tcaactggtcc taggaacaag 480

```

actgaaaatg gactgactcc aaagaaaaaa attcaggtga attcaaaacc ttcaattcag      540
cccaagcctt tattgcttcc agcagcaccc aagactcaaa caaactccag tgttccagca      600
aaaaccatca ttattcagac agtaccaacg cttatgccat tggcaaagca gcaaccaatt      660
atcagttttac aacctgcacc cactaaaggc cagacggttt tgctgtctca gcctactgtg      720
gtacaacttc aagcacctgg agttctgccc tctgctcagc cagtccttgc tgttgctggg      780
ggagtcacac agctccctaa tcacgtggtg aatgtggtac cagccccttc agcgaatagc      840
ccagtgaatg gaaaactttc cgtgactaaa cctgtcctac aaagtacat gagaaatgtc      900
ggttcagata ttgctgtgct aaggagacag caacgtatga taaaaaatcg agaatccgct      960
tgtcagtctc gcaagaagaa gaaagaatat atgctagggt tagaggcgag attaaaggct     1020
gccctctcag aaaacgagca actgaagaaa gaaaatggaa cactgaagcg gcagctggat     1080
gaagttgtgt cagagaacca gaggcttaaa gtccctagtc caaagcgaag agttgtctgt     1140
gtgatgatag tattggcatt tataatactg aactatggac ctatgagcat gttggaacag     1200
gattccagga gaatgaaccc tagtgtgagc cctgcaaatc aaaggaggca ctttctagga     1260
ttttctgcta aagaggcaca ggacacatca gatggtatta tccagaaaaa cagctacaga     1320
tatgatcatt ctgtttcaaa tgacaaagcc ctgatggtgc taactgaaga accattgctt     1380
tacattcctc cacctccttg tcagccccta attaacacaa cagagtctct caggttaaat     1440
catgaacttc gaggatgggt tcatagacat gaagtagaaa ggaccaagtc aagaagaatg     1500
acaataatc aacagaaaac ccgtattctt caggggtgctc tggaacaggg ctcaaattct     1560
cagctgatgg ctgttcaata cacagaaacc actagtagta tcagcaggaa ctcagggagt     1620
gagctacaag tgtattatgc ttcacccaga agttatcaag acttttttga agccatccgc     1680
agaaggggag acacatttta tgttgtgtca tttogaaggg atcacctgct gttaccagct     1740
accaccata acaagaccac aagacaaaaa atgtcaattg tgttaccagc aataaacata     1800
aatgagaatg tgatcaatgg gcaggactac gaagtgatga tgcagattga ctgtcagggtg     1860
atggacacca ggatcctcca tatcaaaagt tcgtcagttc ctccttacct ccgagatcag     1920
cagaggaatc aaaccaacac cttctttggc tcccctcccg cagccacaga ggcaaccac     1980
gttgtcagca ccatccctga gtcattacaa tag                                     2013

```

```

<210> 20
<211> 670
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<223> ATF6

```

<400> 20

Met Gly Glu Pro Ala Gly Val Ala Gly Thr Met Glu Ser Pro Phe Ser
1 5 10 15

Pro Gly Leu Phe His Arg Leu Asp Glu Asp Trp Asp Ser Ala Leu Phe
20 25 30

Ala Glu Leu Gly Tyr Phe Thr Asp Thr Asp Glu Leu Gln Leu Glu Ala
35 40 45

Ala Asn Glu Thr Tyr Glu Asn Asn Phe Asp Asn Leu Asp Phe Asp Leu
50 55 60

Asp Leu Met Pro Trp Glu Ser Asp Ile Trp Asp Ile Asn Asn Gln Ile
65 70 75 80

Cys Thr Val Lys Asp Ile Lys Ala Glu Pro Gln Pro Leu Ser Pro Ala
85 90 95

Ser Ser Ser Tyr Ser Val Ser Ser Pro Arg Ser Val Asp Ser Tyr Ser
100 105 110

Ser Thr Gln His Val Pro Glu Glu Leu Asp Leu Ser Ser Ser Gln
115 120 125

Met Ser Pro Leu Ser Leu Tyr Gly Glu Asn Ser Asn Ser Leu Ser Ser
130 135 140

Ala Glu Pro Leu Lys Glu Asp Lys Pro Val Thr Gly Pro Arg Asn Lys
145 150 155 160

Thr Glu Asn Gly Leu Thr Pro Lys Lys Lys Ile Gln Val Asn Ser Lys
165 170 175

Pro Ser Ile Gln Pro Lys Pro Leu Leu Leu Pro Ala Ala Pro Lys Thr
180 185 190

Gln Thr Asn Ser Ser Val Pro Ala Lys Thr Ile Ile Ile Gln Thr Val
195 200 205

Pro Thr Leu Met Pro Leu Ala Lys Gln Gln Pro Ile Ile Ser Leu Gln
210 215 220

Pro Ala Pro Thr Lys Gly Gln Thr Val Leu Leu Ser Gln Pro Thr Val
225 230 235 240

Val Gln Leu Gln Ala Pro Gly Val Leu Pro Ser Ala Gln Pro Val Leu
 245 250 255

Ala Val Ala Gly Gly Val Thr Gln Leu Pro Asn His Val Val Asn Val
 260 265 270

Val Pro Ala Pro Ser Ala Asn Ser Pro Val Asn Gly Lys Leu Ser Val
 275 280 285

Thr Lys Pro Val Leu Gln Ser Thr Met Arg Asn Val Gly Ser Asp Ile
 290 295 300

Ala Val Leu Arg Arg Gln Gln Arg Met Ile Lys Asn Arg Glu Ser Ala
 305 310 315 320

Cys Gln Ser Arg Lys Lys Lys Lys Glu Tyr Met Leu Gly Leu Glu Ala
 325 330 335

Arg Leu Lys Ala Ala Leu Ser Glu Asn Glu Gln Leu Lys Lys Glu Asn
 340 345 350

Gly Thr Leu Lys Arg Gln Leu Asp Glu Val Val Ser Glu Asn Gln Arg
 355 360 365

Leu Lys Val Pro Ser Pro Lys Arg Arg Val Val Cys Val Met Ile Val
 370 375 380

Leu Ala Phe Ile Ile Leu Asn Tyr Gly Pro Met Ser Met Leu Glu Gln
 385 390 395 400

Asp Ser Arg Arg Met Asn Pro Ser Val Ser Pro Ala Asn Gln Arg Arg
 405 410 415

His Leu Leu Gly Phe Ser Ala Lys Glu Ala Gln Asp Thr Ser Asp Gly
 420 425 430

Ile Ile Gln Lys Asn Ser Tyr Arg Tyr Asp His Ser Val Ser Asn Asp
 435 440 445

Lys Ala Leu Met Val Leu Thr Glu Glu Pro Leu Leu Tyr Ile Pro Pro
 450 455 460

Pro Pro Cys Gln Pro Leu Ile Asn Thr Thr Glu Ser Leu Arg Leu Asn
 465 470 475 480

His Glu Leu Arg Gly Trp Val His Arg His Glu Val Glu Arg Thr Lys
 485 490 495

Ser Arg Arg Met Thr Asn Asn Gln Gln Lys Thr Arg Ile Leu Gln Gly
500 505 510

Ala Leu Glu Gln Gly Ser Asn Ser Gln Leu Met Ala Val Gln Tyr Thr
515 520 525

Glu Thr Thr Ser Ser Ile Ser Arg Asn Ser Gly Ser Glu Leu Gln Val
530 535 540

Tyr Tyr Ala Ser Pro Arg Ser Tyr Gln Asp Phe Phe Glu Ala Ile Arg
545 550 555 560

Arg Arg Gly Asp Thr Phe Tyr Val Val Ser Phe Arg Arg Asp His Leu
565 570 575

Leu Leu Pro Ala Thr Thr His Asn Lys Thr Thr Arg Pro Lys Met Ser
580 585 590

Ile Val Leu Pro Ala Ile Asn Ile Asn Glu Asn Val Ile Asn Gly Gln
595 600 605

Asp Tyr Glu Val Met Met Gln Ile Asp Cys Gln Val Met Asp Thr Arg
610 615 620

Ile Leu His Ile Lys Ser Ser Ser Val Pro Pro Tyr Leu Arg Asp Gln
625 630 635 640

Gln Arg Asn Gln Thr Asn Thr Phe Phe Gly Ser Pro Pro Ala Ala Thr
645 650 655

Glu Ala Thr His Val Val Ser Thr Ile Pro Glu Ser Leu Gln
660 665 670

<210> 21
<211> 36
<212> DNA
<213> Artificial

<220>
<223> Designed polynucleotide based on the base sequence of SEQ ID NO:3
for use as a primer to obtain mature HtrA2 DNA

<400> 21
catatggcgcg tccctagccc gccgcccgcgt tctccc

36

<210> 22
<211> 35
<212> DNA
<213> Artificial

<220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3
 for use as a primer to obtain mature HtrA2 DNA

<400> 22
 ctcgagttct gtgacctcag gggtcacata taagg 35

<210> 23
 <211> 40
 <212> DNA
 <213> Artificial

<220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3
 for use as a primer to obtain mature HtrA2(S306A) DNA

<400> 23
 gctattgatt ttggaaacgc tggaggtccc ctggttaacc 40

<210> 24
 <211> 40
 <212> DNA
 <213> Artificial

<220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3
 for use as a primer to obtain mature HtrA2(S306A) DNA

<400> 24
 ggtaaccag gggacctcca gcgtttccaa aatcaatagc 40

<210> 25
 <211> 39
 <212> DNA
 <213> Artificial

<220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 5 for use as a primer to obtain SHC3 DNA

<400> 25
 ggatccgccg tgcttccacg caccaagtat aaccgcttc 39

<210> 26
 <211> 37
 <212> DNA
 <213> Artificial

<220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 5 for use as a primer to obtain SHC3 DNA

<400> 26
 ctcgagctgc ttcctctcca ctggctgctg gagacac 37

<210> 27
 <211> 27
 <212> DNA

<213> Artificial
 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 7 for use as a primer to obtain CREBL1 DNA
 <400> 27
 gcgaattcgc catggcggag ctgatgc 27
 <210> 28
 <211> 28
 <212> DNA
 <213> Artificial
 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 7 for use as a primer to obtain CREBL1 DNA
 <400> 28
 gcctcgaggg gatgattgag gtagaggg 28
 <210> 29
 <211> 30
 <212> DNA
 <213> Artificial
 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 7 for use as a primer to obtain CREBL1 DNA
 <400> 29
 gcg gatcccg cggagctgat gctgctcagc 30
 <210> 30
 <211> 33
 <212> DNA
 <213> Artificial
 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 7 for use as a primer to obtain CREBL1 DNA
 <400> 30
 cctcgagggt taggatgat tgaggtagag ggg 33
 <210> 31
 <211> 30
 <212> DNA
 <213> Artificial
 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 9 for use as a primer to obtain ATF6 DNA
 <400> 31
 agttccaggg aaaaggaact tgtgaaatgg 30
 <210> 32

<211> 30
 <212> DNA
 <213> Artificial

 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 9 for use as a primer to obtain ATF6 DNA

 <400> 32
 acgctcagtt ttccacatag ctgcgggtgc 30

 <210> 33
 <211> 39
 <212> DNA
 <213> Artificial

 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 9 for use as a primer to obtain ATF6 DNA

 <400> 33
 aaagatatca tgggggagcc ggctgggggtt gccggcacc 39

 <210> 34
 <211> 39
 <212> DNA
 <213> Artificial

 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 9 for use as a primer to obtain ATF6 DNA

 <400> 34
 aaactcgagc tattgtaatg actcagggat ggtgctgac 39

 <210> 35
 <211> 39
 <212> DNA
 <213> Artificial

 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1
 9 for use as a primer to obtain ATF6 DNA

 <400> 35
 aaaagatcta tgggggagcc ggctgggggtt gccggcacc 39

 <210> 36
 <211> 36
 <212> DNA
 <213> Artificial

 <220>
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3
 for use as a primer to obtain mature HtrA2(delta AVPS) DNA

 <400> 36
 gagctcatgc cgccgccgc ttctccccgg agtcag 36

<210> 37
<211> 36
<212> DNA
<213> Artificial

<220>

<223> Designed polynucleotide based on the base sequence of SEQ ID NO:3
for use as a primer to obtain mature HtrA2(GVPS) DNA

<400> 37

gagctcatgg gcgtccctag cccgccgcc gcttct

36